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# Public Health Reports

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## UNITED STATES.

THE ETIOLOGY OF YELLOW FEVER—ABSTRACT OF THE REPORT OF THE COMMISSION OF MEDICAL OFFICERS, MARINE-HOSPITAL SERVICE, DETAILED BY AUTHORITY OF THE PRESIDENT TO INVESTIGATE THE CAUSE OF YELLOW FEVER.

Under date of November 8, 1897, P. A. Surg. (now Surgeon) Eugene Wasdin and P. A. Surg. H. D. Geddings were detailed, by authority of the Secretary of the Treasury and the President, as a commission to investigate in Havana the nature of yellow fever. Their full report, dated July 10, 1899, has been received and is printed as a separate publication.

The report embodies the work of the commission in fairly testing the claim of Professor Sanarelli, of Bologna, Italy, that the bacillus icteroides is the cause of yellow fever, and the conclusion is drawn that this famous scientist has isolated the true cause of the terrible scourge.

This conclusion is based upon a careful bacteriologic study, in the well-equipped laboratory of the Marine-Hospital Service in Havana, Cuba, of 22 cases of disease thought to be yellow fever by the native physicians in attendance.

Of these cases all were seen during the progress of the disease, and in 14 of them the commission concurred in the diagnosis.

Each case was the subject of careful bacteriologic study before and, if practicable, after death. This consisted in the abstraction of blood in sterile bulb tubes from the ear tip under careful asepsis. This blood was then diluted in the bulbs with meat-peptone bouillon, and after an incubation of twenty-four hours the growth was transplanted to fresh

tubes of bouillon, from which, after twenty-four hours, Petri plates were made in series. From these the organisms present in the blood were isolated in pure cultures and studied. After isolation each organism was subjected to the cultural examination on all media, by means of which those meeting the demands of Sanarelli for the organism he discovered were readily selected and their pathogenicity for animals established.

Of the 14 cases diagnosed as yellow fever, the commission isolated the organism of Sanarelli, the bacillus icteroides, from 13, and in the case in which this organism escaped the observation of the commission it was isolated by an independent observer for whom tube cultures had been taken at a necropsy conducted by the commission.

Thus the even percentage of isolations has been obtained in these 14 cases, all of which presented prominent symptoms of the disease. In the cases not thus diagnosed the organism of Sanarelli was not obtained.

From the living blood in 12 of the 14 cases, abstracted not earlier than the third day of the disease, the organism was isolated, and in the 2 others it was obtained post-mortem.

The commission, having preserved a number of cultures made at the isolation hospital in the city of New Orleans from cases seen during the epidemic of 1897, also isolated therefrom the bacillus icteroides in the proportion of 83.33 per cent of the cases examined, the cultures having been made at necropsy.

Thus the identity of the bacillus icteroides of our Southern States, with that found in Cuba, and that sent the commission by Professor Sanarelli, which was obtained in South America, was established.

As a control to these examinations the commission made use of a number of cases suffering from diseases other than yellow fever, from which the blood, extracted in the same manner and treated in the same way, failed to yield any organism at all comparable to Sanarelli's. These diseases were representative of those usual to the city of Havana and were seen during the same period of time in which the cases of yellow fever were under observation. Also there were 31 dead bodies examined, bodies dead from known and unknown diseases, many of them in the city morgue, the most of them in the Spanish military hospitals. In each instance careful section was made and the blood from the heart, from the liver, the spleen, and the kidneys, and the urine, and feces, planted directly into bouillon or agar-agar slant tubes, from which cultures series of plates were made.

All bodies thus examined, at times many hours after death, yielded colonies of various organisms, save one, and this at the time of necropsy was diagnosed pathologically as yellow fever, and was sterile.

In none of these cases of comparative necropsic examination was the bacillus icteroides found—neither in their blood, nor urine, nor feces. Therefore, the commission assumes that the organism of Sanarelli is found only in bodies sick with or dead from the disease of yellow fever,

at the same time conceding that in many of the sick the blood does not yield the germ, and that in the dead it may prove absent only under certain conditions.

Coincident with the above observations the commission carried on the study of the natural history of the organism as to its mode of entering the body, its colonization therein, its toxic possibilities, and its distribution in the organs post-mortem.

Numerous and interesting experiments were made with animals, the commission finding all the animals at its command, such as mice, rats, dogs, cats, guinea pigs, rabbits, and monkeys, quite susceptible to the artificial infections produced by inoculating them under the skin, intra-peritoneally and endo-venously. At the same time it became convinced that the same or very similar results were obtainable by the use of other organisms of different kinds. It found, as had been claimed by Sternberg, that similar clinical and anatomical results could be found after the artificial administration of the bacillus X, as well as that of Havelburg, and of the bacillus coli communis, all of which proved, artificially exhibited, very pathogenic to all animals, and necropsies upon these revealed similar conditions of the organs. Moreover, the toxins elaborated *in vitro* by the above-named organisms, X, Havelburg, and coli communis, and icteroides were precipitated, purified, and tested, comparatively upon animals, with the result that the commission decided that the *mode of death* from these toxins, when injected into animals, *was the same in kind*, and that the toxins differed only in intensity, and that of these the bacillus icteroides produced the most potent.

From these facts the commission, early in its work, became convinced that the claim of Professor Sanarelli, of having discovered the germ of yellow fever, was not established by any evidence presented in his published works, and that it was not tenable so long as it could be claimed that the bacillus of Havelburg and the bacillus X of Sternberg produced the same pathological conditions when artificially inoculated, and the commission recognized the validity of this claim, in view of the facts given above, although it had for a long time recognized both of these organisms as belonging to the colon group.

At this stage of its work the solution of the problem seemed very remote, but before turning to some other and unknown cause of this disease it was determined to place experimental animals under *natural conditions of infection*, since it was recognized that all preceding experimental work was so artificial that it was impossible for the commission to judge of the pathogenic, or rather *specific*, merits of the three prominent organisms.

From this animal experimentation the commission proves the natural specificity of the organism of Sanarelli; the absolute innocuousness of the bacillus coli communis, of the bacillus X, and of the bacillus Havelburg, to even the most susceptible of animals; and a marked degree of similarity in the reaction of these animals (mice) to the *acute*

*infectious organisms*, such as *bacillus typhosus* and *bacillus cholerae suis*, when exhibited to them naturally. The Sanarelli organism is thus eliminated from the colon group and associated with the acute infectious organisms.

The commission recognized that Sanarelli's claim was *only* one of pathogenicity and not of *specificity*; that until such demonstration of specificity there could be no *valid* claim for his organism. This validity the commission believes to have established in the conclusion that the *bacillus icteroides* is "naturally infectious to animals, the degree varying with the species; that in some rodents local infection is most quickly followed by blood infection; and while in rabbits and dogs there is no evidence of this subsequent invasion of the blood, monkeys react to the infection the same as man."

The commission has determined "that the infection takes place by way of the *respiratory tract*," and that the primary colonization in the lungs is responsible for the first evidences of absorptive intoxication such as fever, pains, etc., characteristic of the disease. Also that this primary colonization in the lungs and its poison symptoms may constitute the *entire attack* of the disease in many instances, an attack so light, so ephemeral, that even the most expert diagnosticians may not differentiate them from other ephemera, or poorly marked attacks of allied diseases, as for instance the *dengue*.

Moreover, the conclusion has been reached that what is known in the literature of yellow fever as the "reactionary fever," the "secondary infection" (from germs normal to the body), and the "secondary paroxysm," is due to the passage of the infecting germ, the *bacillus icteroides*, from its primary colony in the lungs into the general circulation, thus producing a "secondary paroxysm" so familiar clinically in all marked cases, unless of the *siderante* type.

This "secondary paroxysm" is then a septicæmic one, and it depends not upon *bacillus coli communis*, or *bacillus proteus*, or upon the micrococci, but upon the further colonization of the specific organism in the blood, thus bearing out Faget's observation that the "*decline*" of the fever, the true "secondary paroxysm," is as *specific* as the "rise," or the primary attack.

The commission recognizes the coincident invasion of the blood by the organisms of the respiratory tract, among which are found colon and proteus, as of possible, it may be of frequent occurrence, or these may invade from the alimentary canal "during the last hours of life," when the mucosa becomes impaired from stasis and this invasion becomes possible, such mixed septicæmiæ being of most severe type and frequently fatal. The commission, therefore, differs entirely from Professor Sanarelli in his theory that the disease of yellow fever is primarily a septicæmia. Indeed, it can scarcely be a matter of surprise that Sanarelli formulated this opinion, seeing that he always produced, with (as he thought) unimportant exceptions, artificial infections

by internal inoculations, which, perforce, must have produced septicæmiæ. Those cases not open to such explanation, which he observed in man, he explained in a still more unsatisfactory way; in fact by the assumption that the germ selected to hide away in the spleen in small numbers during the *whole course* of the disease only to suddenly come forth and produce a septicæmia at its termination.

The commission, therefore, concludes that the theory of Sanarelli in this regard is not sustained by the facts of these cases, and offers the above solution of probably the most widely and generally observed characteristic of yellow fever, the "secondary paroxysm" characterized by a septicæmia.

The theory formulated and expressed by Dr. Sternberg, U. S. A., that the "germinal principle" in yellow fever was to be looked for in the alimentary tract, an opinion evidently dependent upon the well-known influence of the disease upon the organs adjacent and contributive to this tract and portions of the tract itself, as the duodenum, has been found untenable by the commission, since there is no record of anyone ever having isolated the specific germ from the canal save in the case of its presence there through some capillary hemorrhage into its lumen.

The influence of the various disinfecting agents upon the bacillus icteroides has been studied by the commission with an eye to the practical advantages to be derived from a better acquaintance with the organism, and it is found that the organism is readily influenced by the mechanical and chemical agents in ordinary use. Cold, however, is not a factor in this process, for the organism resists the most extensive refrigeration, and no reliance can be placed on this mode of disinfection. On the other hand, the organism is very susceptible to dehydration, and can not withstand artificial drying for more than ten to twelve days, and it is very probable that its susceptibility to *frost* is due to the lessened humidity of the atmosphere at such seasons rather than to the degree of cold experienced. Sunlight is very fatal to this organism, and no doubt is more so if the organism has lost its vitality through evaporation of its fluids, as in a frosty atmosphere.

The resemblance between the bacillus icteroides, in its behavior on certain media, and the bacillus of hog cholera has been brought to the attention of the commission, and it has deemed the observation that there is a possible similarity in the pathogenicity of the two organisms in the domestic hog of great importance, although its experience in the observation of the cultural similarities leads to the conclusion that they are culturally distinct, while the infection of the domestic hog, in its experience, is impossible by the method pursued of feeding bacillus icteroides to them.

However, the question being of too much importance to be determined without full data, the commission placed under treatment a number of domestic hogs, in an environment free from suspicion of the possibility of any contamination with the bacillus cholerae suis, with a

view to deciding the question of the reaction of these animals to the bacillus icteroides, administered to them in pure cultures in their food. These experiments were conducted at the United States quarantine station at Delaware Breakwater, and therefrom it is deduced, first, that the domestic pig is incapable of infection from the bacillus icteroides when introduced through the intestinal or digestive tract, and second, that the bacillus icteroides, when fed to pigs, will not produce any of the lesions or intestinal symptoms of hog cholera.

#### CONCLUSIONS OF THE COMMISSION.

First. That the microorganism discovered by Prof. Giuseppe Sanarelli, of the University of Bologna, Italy, and by him named "bacillus icteroides," is the cause of yellow fever.

Second. That yellow fever is naturally infectious to certain animals, the degree varying with the species; that in some rodents local infection is very quickly followed by blood infection; and that, while in dogs and rabbits there is no evidence of this subsequent invasion of the blood, monkeys react to the infection the same as man.

Third. That infection takes place by way of the respiratory tract, the primary colonization in this tract giving rise to the earlier manifestations of the disease.

Fourth. That in many cases of the disease, probably a majority, the primary infection or colonization in the lungs is followed by a "secondary infection" or a secondary colonization of this organism in the blood of the patient. This secondary infection may be complicated by the coinstantaneous passage of other organisms into the blood, or this complication may arise during the last hours of life.

Fifth. That there is no evidence to support the theory advanced by Professor Sanarelli that this disease is primarily a septicæmia, inasmuch as cases do occur in which the bacillus icteroides can not be found in the blood or organs in which it might be deposited therefrom.

Sixth. That there exists no causal relationship between the bacillus "X" of Sternberg and this highly infectious disease, and that the bacillus "X" is frequently found in the intestinal content of normal animals and of man, as well as in the urine and the bronchial secretion.

Seventh. That, so far as your commission is aware, the bacillus icteroides has never been found in any body other than one infected with yellow fever, and that whatever may be the cultural similarities between this and other microorganisms it is characterized by a specificity which is distinctive.

Eighth. That the bacillus icteroides is very susceptible to the influences injurious to bacterial life; and that its ready control by the processes of disinfection, chemical and mechanical, is assured.

Ninth. That the bacillus icteroides produces *in vitro*, as well as *in vita*, a toxin of the most marked potency; and that, from our present knowledge, there exists a reasonable possibility of the ultimate production of an antiserum more potent than that of Professor Sanarelli.